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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/117,071	09/25/98	KINGSMAN	A	9192.5USWO

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EXAMINER	
LEE, G	
ART UNIT	**PAPER NUMBER**
1632	13

DATE MAILED: 03/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/117,071	Kingsman et al
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

Responsive to communication(s) filed on _____

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

- [X] Claim(s) 22-46 is/are pending in the applicat
- Of the above, claim(s) 26-30 and 35-40 is/are withdrawn from consideration
- [ ] Claim(s) _____ is/are allowed.
- [X] Claim(s) 22-25, 31-34, and 41-46 is/are rejected.
- [ ] Claim(s) _____ is/are objected to.
- [ ] Claims _____ are subject to restriction or election requirement.

Application Papers

- [ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.
- [ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.
- [ ] The specification is objected to by the Examiner.
- [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- [X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
  - [X] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been
    - [X] received.
    - [ ] received in Application No. (Series Code/Serial Number) _____.
    - [ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
  - *Certified copies not received: _____
  - Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- [X] Notice of References Cited, PTO-892
- [X] Information Disclosure Statement(s), PTO-1449, Paper No(s). 8-10
- [ ] Interview Summary, PTO-413
- [ ] Notice of Draftsperson's Patent Drawing Review, PTO-948
- [ ] Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Applicant's election of group I is acknowledged. Claims 22-25, 31-34 and 41-46 are now pending. Claims 1-21 were canceled in Paper No. 6. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03 (a)).

Applicant's amendment filed December 9, 1999 has been entered.

Claims 22-25, 31-34, and 41-46 are currently under examination.

Claim Objections

Claims 41 and 46 have been amended but withdrawn from further consideration for its dependency to non-elected claims 26 and 27, respectively.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C.119 (e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In the instant case, the abstract contains legal phraseology and is missing pronouns required for recitation in narrative form.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 41 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-25, 31-34 and 42-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of packaging a set of DNA sequences

(pHIT456, pHIT111 and pHIT60 vectors) capable of producing the defective retrovirus particles containing a therapeutic gene of interest within a producer cell *in vitro*, does not reasonably provide enablement for inducing any and all cells into a producer cell *ex vivo* or *in vivo* such that expression of any and all therapeutic genes by said replication defective retrovirus in a producer cell inside a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims 22-25, 31-34 and 42-45, as written, read on an *in vivo* or *ex vivo* gene therapy. The claims read on a method of making a producer cell wherein the producer cell contains a set of DNA sequences capable of producing the replication defective retrovirus particle containing at least one therapeutic gene of interest within any and all cell of a patient wherein said cell is the producer cell. The specification discloses that defective retroviruses are used to transduce cells that have been removed from the body (*ex vivo* gene delivery) or they **can** be delivered to tissues *in situ* (*in vivo* gene delivery) (page 3, line 19-21). The specification states that *in vivo* gene delivery is not widely used because gene delivery is inefficient largely because the retroviral particles delivered in this way are rapidly cleared from the site of treatment and there is no extended exposure of the cells to viral particles (page 3, line 25-29). The specification discloses three- plasmids (pHIT456, pHIT111 and pHIT60) in which co-transfections were carried out by calcium-phosphate. Plasmid pHIT60 (MuLV *gag-pol* expression plasmid), pHIT456 amphotropic *env* expression plasmid, and pHIT111 (retroviral DNA construct containing the

lacZ gene) were co-transfected into HT1080 cells (page 14, lines 1-5). From the teachings and examples in the specification, it is apparent that transfection of a set of vectors into cells that are capable of producing a replication defective retrovirus particle, *in vitro*.

However, the claims are not enabled as the specification does not provide guidance as to the amount of producer cells to provide any treatment, amount of DNA sequences to ensure production of a functional replication defective retrovirus particle containing a therapeutic gene, targeting of DNA sequences to efficiently transduce a producer cell within a patient and promoters regulating the expression of any therapeutic gene within any producer cell, either *in vivo* or *ex vivo*, to a subject such that one of ordinary skill in the art could reproducibly and consistently effectively treat the patient in need thereof without undue experimentation.

With regards to treating diseases in general, the specification does not disclosed any treatment methodology *in vivo* or *ex vivo*. The specification on page 8 encompasses a possible use of these sequences containing a suicide gene, i.e. HSV Tk to transduce and transfect cells to be destroyed by treatment with drugs such as acyclovir (lines 9-12). Pages 9 and 10 of the specification teach the advantages in the patient which only considers it to *in vitro* or *ex vivo* methodology such as re-implantation into the patient of the instant invention.

With regard to *in vivo* method of preparing a replication defective retroviral vector in a subject as a method for gene transfer, the specification only provides an example of administration of a set of DNA capable of producing the replication defective retroviral vector in

patient. The specification indicates that administration of a set of DNA capable of producing the replication defective retroviral vector can be directly administered to a target cell within a patient by the direct delivery of appropriate combinations of DNA sequences. A set of DNA capable of producing the replication defective retroviral vector is delivered to the cells by any appropriate non-retroviral method including injection, biolistic delivery, and carry mediated delivery (page 7, lines 32-32). Applicant's specification fails to provide guidance to the skilled artisan on the parameters for gene delivery for enabling disclosure of the claimed invention. Numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level and ratio of each of the set of DNA sequence to produce a functional replication defective retroviral particles, the stability of DNA sequences in order to produced, package a effective replication defective retroviral particles containing a therapeutic gene, the amount and stability of the retroviral particles produced. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable in inefficient. For example, Miller et al reviews the types of vectors available for in vivo gene therapy, and concluded that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review..." which are

currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery system" (page 198, column 1). Deonarain is a 1998 publication which indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al (published in 1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242). Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and the enable the transferred gene to be regulated" (page 409). While applicant's specification supports efficient transfer for *ex vivo* and *in vitro* direct administration into the cells, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved

any mode of delivery of a set of DNA sequences capable of producing a replication defective retroviral particle containing a therapeutic gene. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

Similarly, with regards to *ex vivo* gene therapy strategies for treatment, the specification is non-enabling as the specification does not provide sufficient guidance as to how one of ordinary skill in the art would treat a patient by administering genetically altered cells. The specification does not disclose any specific disease or disorder which has been subjected to the claim-designated treatment regimen, nor does the specification teach any specific methodology associated with such a treatment regimen including the number of cells to be administered for each disease or disorder, the route of administration for each disease or disorder, or the relevant cell therapy target site for the disease or disorder. Moreover, the state of the art at the time of filing suggests that cell transplantation therapies to treat diseases or disorders are neither routine nor predictable. Applicant claims a producer cell for use in treatment wherein the cell is an immune system cell capable of delivering the vector to target cells intended to receive the therapeutically active gene. Applicant's claims are non-enabling because the specification does not provide guidance to the skilled artisan on the parameters for *ex vivo* cell therapy without undue experimentation.

The claims are extremely broad, encompassing any and all cells as producer cells, any and all therapeutic gene and with any and all DNA sequences capable of producing a replication defective retrovirus use in gene therapy, *in vitro*, *ex vivo* and *in vivo*. The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factor (MPEP 2164.01(a)). In view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the production of *in vivo* or *ex vivo* methodology, or promoters or DNA sequences capable of producing a replication defective retrovirus in a producer cell in a patient, the unpredictable state of the art with respect to the parameters of gene transfer, gene delivery, and gene targeting, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 25, 31, 33-34 and 41-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

Claim 22 is vague and indefinite in its recitation of "the cell" because it is unclear what cell is encompassed in the claim. The metes and bounds of the claim can not be determined.

Claim 22 is vague and indefinite in its recitation of "expressing within a producer cell" because it is unclear how the retroviral vector is expressed without a mode of delivery distinctly claimed. The metes and bounds of the claim can not be determined.

Claims 22 and 25 are vague and indefinite in its recitation of "essential for retroviral function" because it is unclear what components of the retroviral function is essential and what is not consider essential encompassed within the claim. The metes and bounds of the claim cannot be determined.

Claims 22, 31 and 42 are vague and indefinite in its recitation of "within the patient" because it is unclear what patient is the claimed directed to implied. The metes and bounds of the claim can not be determined. "The patient" lacks antecedent basis. Is "the patient" the same as "a subject"?

Claim 31 is vague and indefinite in its recitation of "suitable" because it is unclear what factors of the producer cell determines it to be suitable or not suitable for introduction into a patient. The metes and bounds of the claim can not be determined.

Claims 31, 42, 45 and 46 are vague and indefinite in its recitation of "introduction or introducing" because it is unclear how the producer cell is introduced without a mode of delivery distinctly claimed. The metes and bounds of the claim can not be determined.

Claims 31 and 42 are vague and indefinite in its recitation of "capable of" because it is unclear what factors are encompassed within the claims to make the producer cell produce or not produce a replication defective retroviral vector. The metes and bounds of the claim cannot be determined.

Claims 33, 34 and 43 are vague and indefinite in its recitation of "target cells or target cell type" because it is unclear what cell types are encompassed within the claims to make the producer cell a target cell type or not target cell type. The metes and bounds of the claim cannot be determined.

Claims 23, 31 and 42 are vague and indefinite in its recitation of "contain or contains" because the metes and bounds of the claim can not be readily established. In the absence of an express definition in the specification, it cannot be determined if "contain or contains" is narrow or open ended. For examination, it will be given the broadest reasonable interpretation which is open ended. It is suggested that the term "comprises" or "consisting of" be recited instead.

Claim 41 provides for the use of a DNA sequence or set of DNA sequences in the manufacture of a medicament for use in gene therapy, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 34 and 44 are vague and indefinite in its recitation of "capable of" because it is

or not deliver the vector to target cells. The metes and bounds of the claim cannot be determined.

Claims 45 and 46 provides for a method of performing gene therapy, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is practiced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-34 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Garver, R (WO 95/26411).

Garver teaches a replication-defective viruses and means for intracellular replication thereof. Human cells can be changed into recombinant replication-defective virus particle-producing cells by the simultaneous delivery to those cells of two different nucleic acids: the first being a replication-defective viral genome, the second being a nucleic acid that complements the viral sequences deleted from the first nucleic acid so as to result in the production of new infective virus (abstract). Garver further teaches a method of preparing a replication-defective

virus including adenoviruses, herpesvirus, retroviruses, and adeno-associated viruses (p

mammalian cell (abstract and claims). Garver discloses creation of syngeneic recombinant virus-producing cells by cotransduction of trans-complementing plasmid constructs of recombinant retrovirus (pages 44-47, fig. 6B). Thus, Garver clearly anticipates claims 31-34 of the instant invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee

Patent Examiner

Art Unit 1600

Karen M. Hauda

Patent Examiner